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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,027	03/26/2002	William E. Jack	NEB-166-PUS	9409
28986	7590	04/29/2010		
HARRIET M. STRIMPEL, D. Phil. New England Biolabs, Inc. 240 COUNTY ROAD IPSWICH, MA 01938-2723			EXAMINER HUTSON, RICHARD G	
			ART UNIT 1652	PAPER NUMBER
			NOTIFICATION DATE 04/29/2010	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/089,027	Applicant(s) JACK ET AL.	
	Examiner Richard G. Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 32-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 32-43 remain pending and at issue for examination.

Applicant's election of the species of SEQ ID NO: 5, in the paper of 2/11/2008, continues to be acknowledged.

Applicants' filing of an appeal brief on 2/2/2010, is acknowledged. Upon further consideration it has been determined that the following new rejection (based upon 35 USC 103) is appropriate and has resulted in a non-final rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 32-42 under 35 U.S.C. 112, first paragraph, as not containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is hereby withdrawn based upon applicants arguments presented on 2/2/2010.

Claims 32-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising providing a DNA Polymerase selected from the group consisting of Vent, Deep Vent, *Pfu* and 9^oNTM or the specifically disclosed variants referred to in claim 43, with a template, a primer that

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binds to the template and a nucleotide solution containing at least one acyclonucleotide and incubating the DNA polymerase with the template and the nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides, does not reasonably provide enablement for any method comprising providing a DNA Polymerase having an amino acid sequence that shows a mere 30% overall identity with that of SEQ ID NO: 4 and further includes a 15 amino-acid motif that is identical to SEQ ID NO: 5-22 except that it contains up to 3 amino acid substitutions as compared with the SEQ ID NO, with a template, a primer that binds to the template and a nucleotide solution containing at least one acyclonucleotide and incubating the DNA polymerase with the template and the nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection is stated in the previous office action as it applied to previous claims 32-42. In response to this rejection applicants have filed an appeal brief and continue to traverse the rejection as it applies to the claims.

Applicants traverse this rejection on the basis that applicants submit that the Examiner maintains this rejection without offering *any* explanation or support of this position.

Applicants continue to submit that regarding Wands factor 2, amount of direction or guidance, the 15 amino acid motif is a highly conserved motif in the active site of family B DNA polymerases which plays a role in substrate binding and provides the

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necessary direction or guidance. In response to this argument, while the existence of the referred to motif is helpful for identifying those polymerases which bind acyclonucleotides, with in the context of an active DNA polymerase, the existence of this single 15 amino acid motif by itself is insufficient to provide the necessary direction or guidance needed to enable the extreme breadth of these DNA polymerase encompassed by the claimed methods. The existence of 30% overall identity with that of the polypeptide encoded by SEQ ID NO:4 does not sufficiently reduce the size of the claimed genus such that this requirement in addition to the existence of a mere 15 amino acid motif does not provide sufficient direction or guidance as to the breadth of the vast number of DNA polymerases encompassed by these structural limitations, Including both known and unknown DNA polymerases.

As previously stated, Applicants do not teach that DNA polymerases with 30% overall identity with the polypeptide encoded by of SEQ ID NO:4 and including a 15 amino acid motif identical to one of SEQ ID NOs 5-22 (except for having up to 3 amino acid substitutions) can incorporate acyclonucleotides but rather applicants teach that specific DNA polymerases which have as little as 30% identity to SEQ ID NO: 4 and also include a 15 amino acid motif selected from one of SEQ ID NOs 5-22 can incorporate acyclonucleotides. The identification of the species does not enable the extreme breadth of the claimed genus.

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While applicants submit that the specification makes clear that (1) all tested DNA polymerases having the motif have the activity; and (2) DNA polymerases lacking the motif do not. This argument presented by applicants is addressed below.

Applicant's complete argument continues to be acknowledged but not found persuasive for the reasons stated previously and repeated herein. It is admitted that the maintenance of the current enablement rejection may in part be due to applicant's means of claiming applicant's invention.

Without sufficient guidance, determination of those DNA polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

In spite of applicants cited reasons, the rejection is maintained on the basis that applicants have not met applicant's burden with regard to the *Wands* factors for the reasons previously stated.

It continues that applicants have not enabled the scope of the claimed methods on the basis that applicants have not given guidance as to those DNA polymerases which have the ability to incorporate acyclonucleotides into a DNA template. It is noted that applicant's claims encompass not only methods of use of naturally occurring DNA polymerases, but also variants and mutants thereof. As discussed above and previously, applicants have merely identified a few specific DNA polymerases within the 30% sequence identity range that have the necessary acyclonucleotide incorporation

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function. Such does not enable the breadth of the claimed subgenus of methods of use of the encompassed DNA polymerases which encompasses not only the use of naturally occurring DNA polymerases but also variants and mutants thereof. It remains that applicants have not enabled the extreme breadth of those DNA polymerases so encompassed. Applicants have not enabled the breath of those methods of incorporating acyclonucleotides comprising the use of those DNA polymerases having a mere 30% identity to that polypeptide encoded by SEQ ID NO: 4 and comprising a motif that is selected from the 18 different amino acid motifs listed in SEQ ID NOs: 5-22 and variants thereof.

As previously stated, with regard to applicants argument regarding the identification of an amino acid motif domain that is required for this specific function of acyclonucleotide incorporation, it is noted that applicants specification at page 19, lines 22-24, does not clearly support such. The clarification or expansion of applicant's argument regarding this reference to "the motif" on page 8, line 7 of applicant's argument submitted on 1/9/2009, might be helpful in overcoming this rejection if the referred to "the motif" is shown to correlate with the incorporation of acyclonucleotides. To date this showing has not been clearly established and as such applicants have not enabled the currently claimed methods beyond the taught species. One of the reasons it appears that applicants have not established a correlation between a motif and the acyclonucleotide incorporation function, appears that applicants have not disclosed such a single motif but rather continue to refer to any of a number of motifs or variants thereof.

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Beyond the above, without sufficient guidance, determination of those methods and polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 32- 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Koster et al.* (U.S. patent No. 5,928,906, See IDS submitted on 5/13/2008) and *Reid et al.* (Journal of Biological Chemistry, Vol 263, pp3896-3904, 1988, See IDS).

Koster et al. teaches a process for direct nucleic acid sequencing during template amplification. *Koster et al.* specifically teaches such a method comprising contacting a nucleic acid template with a Vent DNA polymerase (which is encoded by SEQ ID NO:4 and includes a 15 amino acid motif of SEQ ID NO:5) and a collection of nucleotides and a chain terminating dideoxynucleotide and incubating the DNA polymerase with the template and nucleotides so that the DNA polymerase extends the primer by

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incorporating the nucleotides. Koster et al. does not teach the use of an acyclonucleotide as a chain terminating acyclonucleotide.

Reid et al. teach studies of the insertion and extension of acyclic, dideoxy and ara nucleotides by various DNA polymerases including Herpesviridae, Human α and Human β polymerases. Reid et al. specifically teach a method of analysis of the insertion and extension of various chain terminating nucleotides including dideoxynucleotides and acyclonucleotides comprising contacting a DNA polymerase with a primer that binds to a template and a collection of nucleotides including an acyclonucleotide and incubating the DNA polymerase with the template and nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides.

One of ordinary skill in the art at the time of filing would have been motivated to practice a method comprising providing a vent DNA polymerase, as taught by Koster et al. and contacting the vent DNA polymerase with a template, a primer that binds to said template and a collection of nucleotides and an acyclonucleotide as taught by Reid et al. and incubate the DNA polymerase and template and nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides, in order to determine the feasibility of using the chain terminating nucleotide, acyclonucleotide, in sequencing methods with vent DNA polymerase. The expectation of success is high as everything that is required to perform the made obvious method is taught by the references of Koster et al. and Reid et al. and the made obvious methods do not require any specific result, but merely the motivation to bring the components of the reaction together and "incubate".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rg
4/13/2010

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